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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/791,753	03/04/2004	Tsutomu Fujimura	249976US0	5264

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EXAMINER	
LEITH, PATRICIA A	

ART UNIT	PAPER NUMBER
1655	

NOTIFICATION DATE	DELIVERY MODE
02/02/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/791,753	FUJIMURA, TSUTOMU	
	Examiner	Art Unit	
	Patricia Leith	1655	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-25* is/are pending in the application.

4a) Of the above claim(s) *1-3,5,9,11 and 13* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,6, 10, 12 and 14-15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/30/09*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 11/13/09 has been entered.

Digenea simplex may be referred to herein as 'DS.'

Status of the Claims

Claims 1-6 and 9-25 are pending in this application.

Claims 1-3, 5, 9, 11 and 13 remain withdrawn from examination as being directed toward a non-elected invention

Claims 4, 6, 10, 12 and 14-25 were examined on their merits.

Declaration

The Declaration submitted by Tsutomu Figumura under 37 CFR 1.132 on 11/13/2009 was fully considered, and will be discussed *vide infra*.

Rejections Removed

The previous rejections instituted in the final Office action under 35 USC 103(a) are herein removed due to Applicant's amendment to the claims to require that the *Digenea simplex* material used is an aqueous/ethanol extract of DS. Additionally, the Declaration filed on 11/13/09 demonstrates that agar (an extract of *Digenea simplex*) as disclosed by Lopes, does not have an ability to increase the expression level of Rho kinase. Although the claims also state that the agent may enhance myosin light-chain kinase, and the Declaration does not show that DS *does not* enhance myosin light-chain kinase, the claims, as they are amended, read an aqueous/ethanol extract of DS which is not considered 'agar' and has been determined to be non-enabled in light of the Declaration as well as the teachings or lack-thereof in the specification as will be keenly discussed *infra*.

It is noted however, that Applicant's arguments pertaining to wherein agar-agar is not *Digenea simplex* are not found persuasive. Applicant's remarks do not negate the fact that *Digenea simplex* contains *Digenea simplex* mucilage which is the same as

agar or agar-agar. While other types of algae may also produce agar as asserted by Applicants (i.e., p. 8, Remarks), Sigma Aldrich makes clear that *Digenea simplex* mucilage is agar, or 'agar-agar' and hence, is the same substance whether produced by *Digenea simplex* or another algae. That being said, the rejection under 35 USC 103(a) has nevertheless been removed due to Applicants' amendment to the claim which is no longer directed toward agar, but to an aqueous ethanol extract of DS.

The previous rejection instituted under 35 USC 112 First paragraph, Written Description has been removed in light of Applicant's convincing arguments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 4, 6, 10 and 14-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in

the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention and (2) the breadth of the claims:

The claims are newly drawn to a method for treating aging of the skin by contacting the skin of a person having symptoms of such with a skin treating agent possessing the ability of increasing an expression level of Rho kinase or myosin light-chain kinase; whereby this agent, as required by the claims, is an aqueous ethanol extract of *Digenea simplex* (DS).

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

The state of the art is unpredictable. Applicant Fijimura provides data present in the Declaration of 11/13/2009 which demonstrates that agar-agar, otherwise known as *Digenea simplex* mucilage, does not provide for enhanced Rho kinase levels *in-vitro*. It is noted that Applicants have amended the claims to require that the *Digenea simplex* is not any extract (which would read broadly on agar which may be obtained from DS), but rather, an alcohol/water extract of *Digenea simplex*.

The state of the art recognizes that skin wrinkles are "..one of the most difficult problems for aesthetic treatment" (quote by Dr. Vince Afsahi; Obesity, Fitness & Wellness Week, Atlanta, GA; June 9, 2007, pg. 466, pp.1-2 of ProQuest). Hilton: CONSUMERS ILL-INFORMED ABOUT ANTI-AGING OPTIONS; Dermatology times, July 2004, 25:7, pp. 58 and 61) cites a dermatologist, who states that "Everyone has

always wanted a cream in a tube to make their wrinkles go away. There has never been anything that comes close to doing that, but if there is something that is new and says that it is going to do it, then it is going to sell. To me, it is kind of like the old hair tonic." (see e.g. page 61). Thus, it is clear that in the dermatology field, cosmetic treatments for wrinkles are not widely accepted as effective means of reducing wrinkles. Therefore, in order to demonstrate effectiveness, claims to treatment for aesthetic conditions such as.wrinkles must find adequate support in the specification and/or the prior art to be enabling.

Additionally, the state of the art indicates that pharmaceutical treatments using plant extracts are unpredictable. *Digenea simplex*, being an algae, is a type of plant, as it is classified under the Kingdom of Plantae. The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24

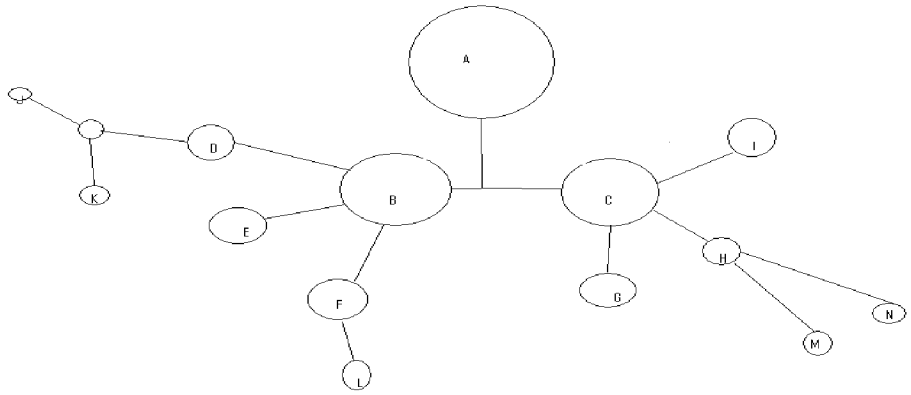
(CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993*); In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work (see MPEP § 2164.04)

It is well known in the art that polarity of solvents plays a key role in determining the final product obtained by an extraction. However, because many phytochemicals remain undiscovered, the skilled artisan has to make his best educated guess as to what types of phytochemicals will be successfully extracted with a solvent of a particular polarity. Often times, unless the constituents in a particular plant extract have been well evaluated and documented in the literature, the skilled artisan must adhere to trial and error protocols in order to quantitatively determine phytochemical constituents present in samples obtained from respective extraction procedures. These procedures are common when, for example, a plant or part thereof has been documented in the literature as possessing some medicinal quality. The skilled artisan will attempt numerous extraction protocols in attempt to isolate the particular ingredient which has this medicinal quality. Typically, beginning with the first crude extraction, it is a guess as to weather or not the extract will possess certain phytochemical constituents. It is noted that the Instant specification does not disclose what the active ingredient of the extract is. Not that such a disclosure is necessary; however, if it were known that the extract of DS as claimed in Applicant's method contained an ingredient which would be

known to be useful in treating wrinkles, such knowledge would invariably lend some predictability to the method.

Each successive extraction of plant matter yields different products due to the exclusion of ingredients based on the polarity of the solvents solvating constituents with similar polarities. Subsequently, the properties of each respective product are unpredictable and would need to be evaluated for chemical constituents. The following is an illustrative example of the many products which may be produced by different successive extraction

protocols:



In this example, assume that A= the initial water extract from a homogenized

sample of grape. The water extract from the grape is then subjected to a methanol/water extraction to form products B (soluble with methanol) and C (more soluble with water). Product C is then extracted in a seperatory funnel with three organic solvents: chloroform, benzene and ethyl ether to form products G, H and I which solvate with the respective solvents based on the polarity of the inherent constituents. Product H, which we will assume is the product obtained in the benzene fraction, is extracted again in a seperatory funnel with benzene and methanol to remove any residual methanol-soluble constituents. The additional circles represent extractions which may be done to obtain different products, using similar solvents as discussed previously, or entirely different solvents. Consequently, the characteristics of each respective product would need to be evaluated for chemical constituents. This representation is indicative of the vast array of distinct products which may be obtained due to the ***enormity of possible extraction permutations***.

Unpredictability with regard to plant extracts due to their highly complex nature has been well documented in the art. Revilla et al. for example (1998) showed that the ***slightest variations in polarity of solvent and reaction time*** upon grape extraction provided respective products with unique characteristic properties (See Tables 1, 2, 4, 5, 6 and 7). In turn, each product would possess varying pharmacological properties based upon their respective methods of extraction.

Further contributing to the unpredictability of plant extracts, it has been

determined that in some cases, the active agent is not a single ingredient, but a combination of ingredients working synergistically to provide a therapeutic effect:

> "The blood red sap from the bark of several species of Croton (Euphorbiaceae) are used in traditional medicine in S. America to treat wounds and a series of diseases including cancer. More than 90% dry weight of the sap consists of mixtures of proanthocyanidins ranging from monomers to heptamers and even to polymers of twenty units. We have established the chemical structures of these oligomers and the monomeric units are either catechin or gallocatechin…In addition, we isolated some novel diterpenoids and a series of simple phenols as minor constituents. As a result of biological tests we have concluded that here is no single ingredient for would healing but that the whole sap contributes to the healing process" (Phillipson, J. 1999).

Accordingly, each product obtained from an extraction is unpredictable in nature and could not be assumed to possess pharmaceutical capabilities. Thus, even the most skilled of artisans would need to quantify each respective extract for medicinal efficacy.

The prior art does not recognize that *Digenea simplex* aqueous/ethanol extracts would be even relatively useful for treating aging of the skin such as wrinkles. Furthermore, Applicant has not elucidated any active ingredient(s) from an aqueous/ethanol extract of DS which could be predictably understood to give the extract any positive effect on treatment of skin wrinkles/sagging. While Applicant demonstrates

on page 23 of the Specification that DS ethanol/aqueous extract has some apparently small effect on increasing Rho kinase expression *in-vitro*, Applicant did not chose this plant extract for testing and thus did not confirm that this extract possesses any activity which would be considered beneficial for treating wrinkles. The small effect on Rho kinase activity attributed to the DS extract, cannot be reasonably extrapolated to any effectiveness toward wrinkle treatment considering the unpredictability of the state of the art coupled with Applicant's own data which will be discussed more keenly, *infra.*

Thus, the claimed method is highly unpredictable.

(5) The relative skill of those in the art:

The relative skill of those in the art is high.

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided data which shows that the aqueous/ethanol extract of DS has some, apparently small, ability to increase Rho kinase expression *in-vitro*. However, Applicant has not stated that this small amount of Rho kinase modulation would be clear indication that the DS extract would in-fact beneficially treat wrinkles. On the contrary, this extract of DS was not tested to confirm the ability of this

extracts to treat wrinkle, sagging or loss of skin elasticity which is required by the claims.

The extracts which were tested for their ability to decrease wrinkles in mice (considered an appropriate model) are the following:

Plant extract	MLCK EA	RK EA	RK-C	WS
Gentiana lutea	139/178	231	123	0.31
Athaea officinalis	100/167	175	75	0.24
Fucus vesiculosus	N/A	145	45	1.04
Curcuma longa	N/A	207	107	0.51

MLCK EA = myosin light-chain expression ability taken from Table 2, page 21 of the specification

RK EA= Rho kinase expression ability taken from Table 3, page 23 of the specification

RK-C = Rho Kinase expression ability – Control Rho Kinase expression ability as calculated, given the data present in Table 3, page 23 of the specification

WS = Wrinkle Score as provided in Table 5 (compared with the control), page 27 of the specification

It is first noted that the values present in table 5 of the specification have considerable overlap (between before and after data) and none of the data is found to be significant.

Secondly, it is clear from Table 5 that *Fucus vesciculosus* scored highest among the extracts tested, specifically giving a final score of 1.8 ± .2739. However, notably, *Fuscus vesciculosus* was not recorded as having any MLCK EA and also, this plant extract possessed the lowest ability, amongst the plant extracts chosen for *in-vivo* testing, for expressing Rho kinase. The data provided by Applicants demonstrates that the wrinkle-treating ability of the plant extracts is not solely manifested from their kinase-activating ability. To the contrary, the data provided by Applicants unequivocally demonstrates the unpredictable nature of plant extracts for treating wrinkles and the unpredictability of using kinase activity as a determinant in choosing an effective plant extract for wrinkle treatment. It is *a priori* clear, that no matter what kinase ability is present (i.e., MLCK or RK) this is not an indication that a plant extract will have the ability to effectively treat wrinkles.

Further, the lowest value of 1.8 ± .2739 equates to, as interpreted by the wrinkle scores given on p. 26 of Applicant's specification, as being observed as weak to moderate. This, again, relying on the data given by Applicant, is not a significant change from the beginning evaluation (of *Fucus vesiculosus*) which was observed as

weak to moderate (again, there is severe overlap between the beginning and end data). Again, all of the data in Table 5 have considerable overlap and no data is found significant.

Hence, it cannot be absolutely concluded that the plant extracts tested *in-vivo* had any ability to manifest a change in wrinkles which would be considered efficacious. Moreover, considering the unpredictable nature of treating wrinkles and the unpredictable nature of plant extracts as keenly discussed by the Examiner and as supported by Applicant's own data, there is no reasonable scientific means to extrapolate a beneficial result of DS extracts on wrinkle treatment given only the Rho kinase expression data provided in the specification.

(8) The quantity of experimentation necessary:

Considering the state of the art as discussed above, and the high unpredictability and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the claimed invention.

The Specification does not show any *in-vivo* examples where wrinkles, sagging or loss of skin elasticity has been treated with an aqueous/ethanol extract of DS.

Applicant's data presented in the Declaration provides evidence of unpredictability with regard to *Digenea simplex* and modulation of rho kinase activity as it is clearly demonstrated in the Declaration that the extract of *Digenea simplex*, said extract being agar, will not provide for the claimed effects. These considerations, coupled with the clear unpredictability in the art with regard to plant extracts used medicinally and also with regard to treatment of wrinkles, in addition to the clear unpredictability of plant extracts in treating wrinkles, independent upon their ability to activate kinases render the claimed invention non-enabled.

In order to perform the methods as Instantly claimed would not just require a repetition of Applicant's work, but would entail a considerable amount of inventive contribution on the part of the skilled artisan involving undue experimentation. This experimentation would be undue considering that the skilled artisan would not have any reasonable expectation of success in carrying out the claimed invention due to lack of guidance in the specification with regard to the efficacy of the composition of the claims toward the claimed ailments as well as lack of teachings in the art with regard to the effectiveness of the claimed composition toward all of the claimed ailments.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Patricia Leith whose telephone number is (571) 272-0968. The examiner can normally be reached on Monday - Friday 8:30am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Terry McKelvey can be reached on (571) 272-0775. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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